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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The aims of this work are to explore the feasibility of developing a *new class* of computer assisted diagnostic (CAD) methods for microcalification cluster (MCC) detection for breast cancer screening using digital mammography. The objectives are to achieve: (a) improved CAD performance that is significantly more robust for large image databases, and (b) an *adaptive* CAD method that is independent of the digital sensor resolution and gray scale characteristics; for the first time.

The proposed method is novel in concept and is based on pioneering experience in development of adaptive CAD algorithms including linear wavelet transforms and non linear transforms for improved feature extraction, their implementation of filter banks that uniquely allow adaptive approaches, and experience in specialized multi-stage neural networks for detection of MCC's with different feature input strategies. The intent is to compare existing wavelet methods to the proposed new method and evaluate them for a *common case* data base using a state of the art direct digital detector and film (three digitizers)

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Introduction:

The aims of this work are to explore the feasibility of developing a *new class* of computer assisted diagnostic (CAD) methods for microcalification cluster (MCC) detection for breast cancer screening using digital mammography. The objectives are to achieve: (a) improved CAD performance that is significantly more robust for large image data bases, and (b) an *adaptive* CAD method that is independent of the digital sensor resolution and gray scale characteristics; for the first time. This report includes 2 sections, **(1). Summary of the work in first year, which includes data base collection and truth file establishment for different sensors, preprocessing for breast area segmentation, and basic algorithm design, (2). Algorithm design and optimization,** which includes a design of a successful MCCs detection system containing the design and optimization of all modules. The detail of our progress is summarized in our recent publications [1, 2, 3, 4, 5]. *A CAD method with improved and robust performance is required for both retrospective studies and an steps towards a more generalizable CAD method, which is critical for multi-center clinical trials.* The proposed method is novel in concept and is based on pioneering experience in development of adaptive CAD algorithms including linear wavelet transforms and non linear transforms for improved feature extraction, their implementation of filter banks that uniquely allow adaptive approaches, and experience in specialized multi-stage neural networks for detection of MCC's with different feature input strategies. The intent is to compare existing wavelet methods to the proposed new method and evaluate them for a *common case* database using a state of the art direct digital detector and film (three digitizers).

BODY OF REPORT

I. Summary of the work completed in the first year of the project

(a). Data base collection and truth file establishment for three sensors

In order to make the CAD algorithms for clinical use, the extensive tests of our algorithms are necessary for larger database from different digitizers with different resolutions. The films of the two sets of 200 views was digitized with two different digitizers: **(a)** a CCD-based system (ImageClear R3000, DBA Systems, Inc, Melbourne, FL) maximum resolution at 30 m and 16 bits and **(b)** a LUMISCAN 85 (Lumisys, Sunnyvale, CA) at maximum resolution, at 50 m, and 12 bits. Digitized images will be acquired at 50 microns with one set transformed to 100microns respectively. And another one set from direct digital mammography system from General Electric which was installed at the H. Lee Moffitt Cancer Center and Research Institute (MCCRI) at USF in June 1998. The direct digital images have a spatial resolution of 100 μm and 12 bits per pixel.

(b). Preprocessing for breast area segmentation

Except a few digital mammogram images are with high quality, most of them suffer from more or less extrinsic signals such as images of edges of original X-ray pictures, or large bright regions caused by the cutting of them, various notes made by doctors, uneven illumination, blurred edges due to the exposure of pictures. Sometimes such extrinsic signals in the digital mammogram images may affect the detection result seriously. In the first year, we developed an algorithm to erase the extrinsic signals. They are helpful for the detection.

(c). Basic algorithm design

Basic algorithm design includes nonlinear bank filter design, implementation and segmentation algorithm design and testing. The nonlinear filter design is based on multiresolution techniques. In the first year of the project, we have tested 20 different segmentation algorithms on MCCs segmentation, such as Relaxation, Digital Desk - adaptive, Fuzzy sets, Otsu's method for grey level histograms, iterative selection, Johannsen Kapur method for using entropy, two histogram peaks, Minimum error and mean, Black percentage, Pun method for using entropy, two histogram peaks, etc.

II. Algorithm Design and Optimization in the current funding year (second year)

(a). Concise technical review for our research background

A successful MCC detection scheme should consist of several modules aiming at solving different kinds of signal processing problems [7-11]. All published work can be grouped in the following five-step paradigm: (1) breast area segmentation and artifact elimination, (2) MCC structure and normal tissue enhancement, (3) suspicious MCC area segmentation or localization, (4) feature extraction and analysis of suspicious areas, and (5) suspicious area classification as normal or abnormal. Most of the work in the literature addressed only one subset of these procedures and some approaches reorganized these steps [10], [12], [13], [14-23]; *i.e. rather than a holistic approach in this work.* Efforts at enhancing microcalcification structures to refine digital visualization [24]-[26] can be also be incorporated in the above paradigm.

Enhancement methods. All the microcalcification enhancement methods can be considered as a simple matched filter or spot detector conducted either at only *single or multiple scales* [8], [10], [16]-[18], [24], [27]-[29] . These methods are generally not robust or generalizable for the work proposed here(C and N). The enhancement step is important to maintain high detection sensitivity and low FP rate.

Segmentation methods. The segmentation can be divided into: (a) global segmentation, which should be considered as suspicious microcalification localization and mostly realized by simple empirical thresholding [8], [14]-[18], [28], and (b) local segmentation directed at keeping geometrical features of each microcalcification [8], [14]. The general criterion for global segmentation is to get a detection result, i.e., in most cases a set of segmented areas, with acceptable sensitivity and false positive distribution for further classifications. We proposed to take more advanced global and local segmentation method.

Feature extraction. In general, feature extraction methods can be divided into implicit approaches training with ROI's within a single image as inputs to a NN [9], [10], [13], [30]-[32] and explicit approaches using indexes calculated from segmented regions or group of regions(ROIs) [8], [12], [21], [23], [33], [34], [37]. *Implicit Features*: There are several problems with implicit feature extraction, i.e., difficulty in incorporating clinical knowledge into the classification and difficulty in deciding ROIs size. *Explicit features:* Their extraction suffers from the limitation of feature design procedures based on human observation and clinical knowledge, which may ignore certain useful visual information. *All the approaches in the literature use either implicit or explicit feature extraction scheme, and are not optimized in a combined way for MCC detection.* Some methods use very small sets of features. Some features are used only at single microcalcification level, instead of the cluster level. Studies aimed at discrimination of microcalcifications and similar normal tissues are rare and coarse [33]. *There does not exist an approach for using both advanced feature extraction methods and inter-projection reference information, the latter is used radiologists to interpret an abnormality in mammograms [35], [36].*

Classifier Design. Design of classifiers is closely related to the feature extraction. A successful system requires a nonlinear feature combination mechanism. More advanced NN techniques are preferable to linear discriminant analysis and rule-based methods [37], [32]. *Mutistage based NN approaches, combining both explicit and implicit features at different stages should prove to be more robust than either only implicit or only explicit feature based approaches .*

CAD parameter optimization. Reported methods are all based iteratively changing CAD parameters, such as image preprocessing and segmentation parameters, and manually generating computed FROC curves; a very time consuming process. *We have recently developed a fully automatic method for this optimization, including parameter changes within a parameter range as opposed to fixed parameters for adaptive CAD methods, together with generation of computer FROC and ROC analysis curves. This is a highly efficient optimization method critical to meet the objectives of this proposal.*

(b). Algorithm Design and Optimization for proposed project

1. Introduction. The research efforts involve design and optimization of all CAD modules as illustrated in Fig 1. We first implemented a robust CAD module of breast segmentation, already developed, that is generalizable to different sensors, a modification of a reported method. We then focused on the design and optimization of nonlinear filter banks based methods for MCC enhancement. This should be optimized to maintain a high detection sensitivity and low false positive rate. A CAD module for MCC identification criteria, which is an extension of previous work [38], should be modified for more accurate cluster extraction from binary images. Extraction of explicit features (inter-projection) should be greatly emphasized and as extension of our work on implicit features . Existing multistage based NN methods will still be adopted and optimized by using input both implicit and explicit features at different stages.

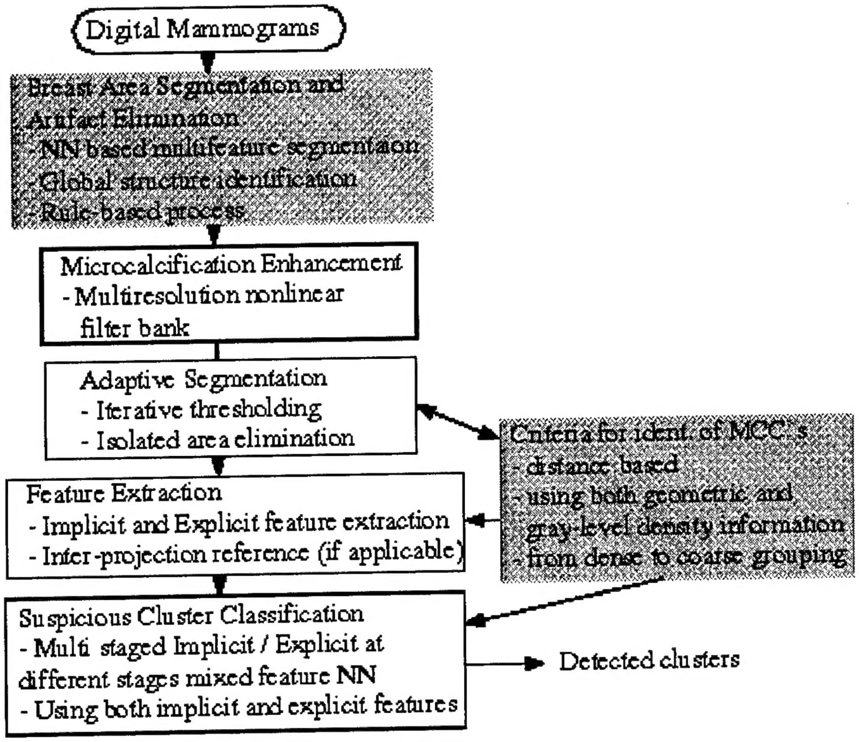

Fig.1. Block Diagram of the MCCs Detection System, Shaded areas have been fully completed. Preliminary progress has been made for all other CAD modules.

2. Multiresolution microcalcification enhancement. The basic structure of the proposed enhancement filter is similar to [29] and is shown if Fig.2a. The terminology for parameters is the same as [29]. The method is mathematically complex and is only briefly described here. Modifications proposed is the use of a multiresolution *nonlinear* filter bank, as shown in Fig. 2b., to replace a tree structured wavelet transform implemented on a linear filter bank, described in [29]. We have already done very preliminary testing of this method on simulated images and a representative mammographic image at 60 micron images, with a biopsy proven MCC's as shown in Fig 3, where details of microcalifications were better preserved than using the 4 channel wavelet transform. *The feasibility of the method has been demonstrated.*

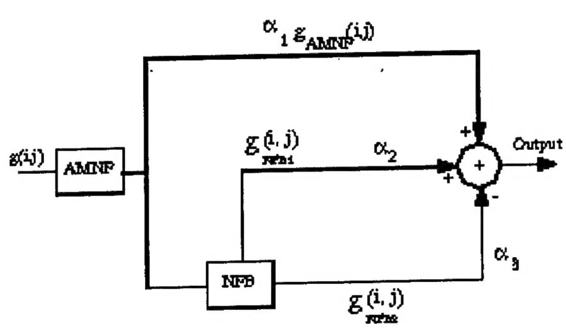

Fig.2a. Image enhancement scheme using hybrid adaptive multistage nonlinear filter (AMNF) and multiresolution nonlinear filter bank (NFB), where NFB is shown in Fig.2b.

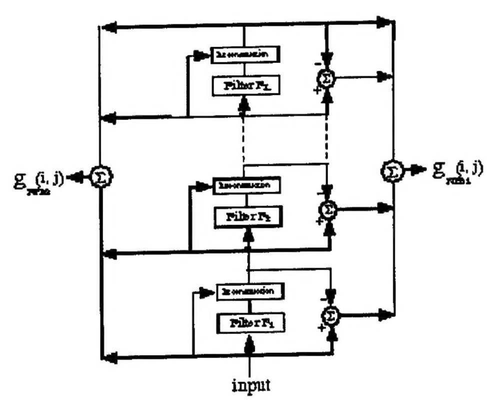

Fig.2b. Multiresolution decomposition scheme with reconstruction using nonlinear filter bank (NFB). g_{NFB1} is the segmented results and g_{NFB2} (I, j) is the background image.

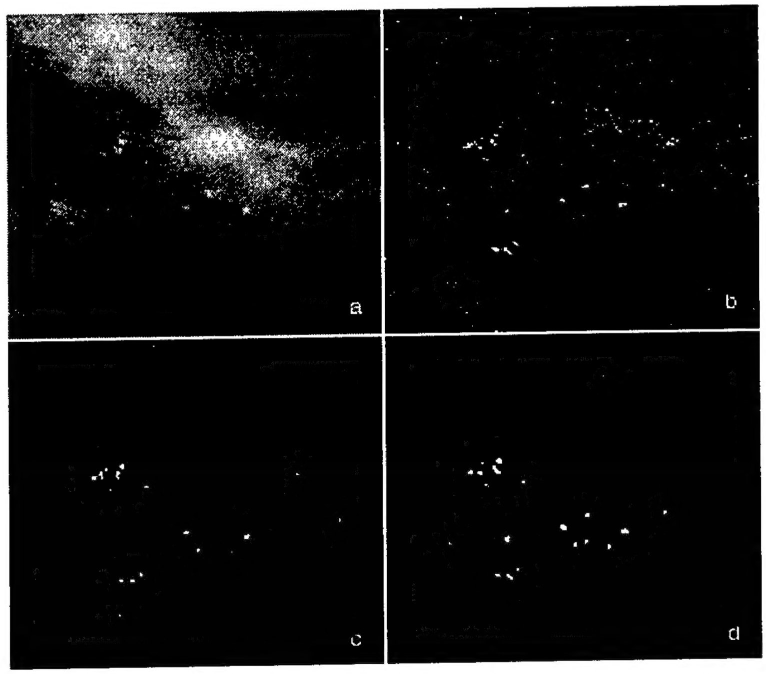

Fig.3. Representative result for MCCs segmentation of a subsection of a mammogram image (60 μm resolution) containing 1 biopsy proven cluster; (a) Raw image, (b) and (c) 2 and 4 channel wavelet transform method respectively, and (d) preliminary data for non linear filter bank. Result in (b) and (c) do not fully delineate the cluster, preserve details of microcalcifications, or have too high FP detection rate. The method in (d) is not fully optimized and does not include all proposed CAD modules.

3. Criteria for identification of clusters. The measured performance of CAD methods for MCC detection is dependent on the specific criteria for identification of the "group of microclassifications" as a cluster. This has recently been addressed in a recent mammography workshop by Clarke and Nishakawa [6]. *We proposed a distance-based area grouping method, instead of the commonly used kernel-based method, to avoid the problems of selection of kernel size and shape. We developed a method based on distance-based and from dense to coarse grouping strategy, this work has been submitted for publication and is attached [38].* Since we propose to evaluate the *relative performance* of the proposed adaptive CAD with a previously reported method[38], the impact of which criteria is not so critical.

4. Adaptive Method for MCC Segmentation. Segmentation methods generally used a fixed threshold for the full mammogram or an adaptive method to the full mammogram to segment MCCs. These methods are not optimum for FP reduction , especially for subtle MCCs. We propose to modify an existing method that is adaptive and iterative, where the criteria is unique. Preview methods generally focus on simple feature related criteria. The steps are as follows. First, segmented image is obtained for a given gray level threshold. If the clusters are larger than a geometrical criteria (i.e. fixed area: 1.5 x 1.5 cm) the threshold can be changed until the creterial is fully contained within this area. The process can be conducted in the inverse direction and the threshold adjustment step can be changed iteratively. This segmentation process directly eliminates the isolated areas. One solution to be investigated is to categorize image regions into several levels by a *global* segmentation. These regions may have some overlaps and the same *adaptive* MCC segmentation scheme can be used in all these regions. Since this segmentation scheme may control the FPs to manageable rate, the result obtained by adding segmented areas from different regions together may be suitable for further processing.

5. Feature extraction. This research step will mainly address explicit feature design and extraction. Implicit features, calculated within a single region of interest (ROI) as reported in the literature and used in our earlier work will be investigated, they include (1) microcalification(s) area, (2) mean intensity, (3) deviation of intensity, (4) average edge gradient, (5) line-likeness, (6) contrast, and (7) number of MCC areas. They will be calculated from the original and enhanced image. We will also explore the use of generic algorithm(GA) for feature selection ranking but may defer most of this optimization step for the ROI proposal. The explicit features proposed include:

- extracting features from multiple domains, such as intensity, geometric.
- extracting both local features and global features, i.e., single calcification level, cluster level and more extended regional level.
- using multi-view reference information [35],(i.e., between CC view and ML view); statistical analysis combined with special case analysis, a specific-to-general philosophy.

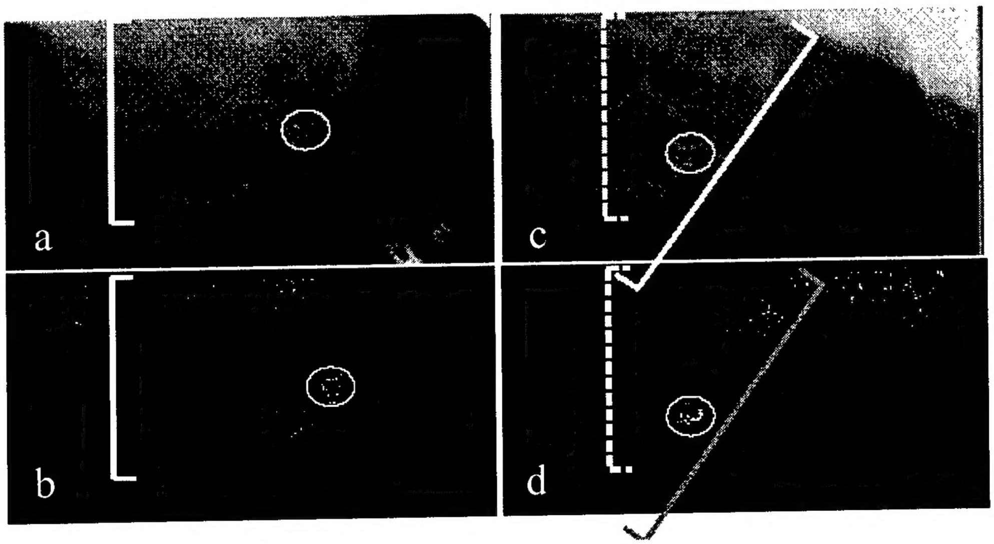

Fig.4. preliminary data for Inter-projection matching using pectoral muscle line as a proposed landmark. (a) and (b) are a CC view image and corresponding segmentation result and (c) and (d) are those for ML view. The true cluster is marked by a circle in each image. Dashed rulers in ML view images mark a wrong alignment direction for find relative positional correspondence. True cluster may possibly keep its distribution and shape patterns in two different views in which the breast was compressed differently during the imaging process. (Segmented areas are slightly dilated for rescaled presentation purpose.)

6. Correlation of Inter-projection features. We will also explore inter-projection reference features, for suspicious cluster classification to improve detection sensitivity and reduce FP rate. The most difficult problem for using two-views (CC and ML) is the spatial matching between clusters. Since the breast is compressed, an exact alignment between two views may be impossible. In preliminary data we have found that the spatial correlation for two views along antero-posterior direction. As shown in Fig. 4, if the suspicious areas are found in upper parts of the views, the positional coherence should be approximately along Y-direction of images. Based on a feasible study over a considerable number of images, the Y-axis in CC view was found to correspond to the direction perpendicular to the pectoral muscle line in ML view; will play a key role in aligning the two views(Fig. 4). A matching procedure will be therefore proposed to match the set of clusters in one view as above using relaxation labeling techniques [39]. Additional explicit features will be explored such as similarity measurements between two clusters from the two views. They include : (1) Positional similarity, (2) Cluster size similarity, (3) Similarity of calcification number, (4) Similarity of average

calcification area, (5) Similarity of average intensity deviation within calcification areas, (6) Similarity of average elongation of calcification areas.

7. Classifier design. The classifier must combine both implicit and explicit features. To combine a considerable number of features is very difficult to realize in an analytical way and neural network methodologies have the advantages in dealing with this kind of nonlinear optimization problem through training procedures. Modifications to the NN design is required to address the great number of input nodes. A multistaged mixed feature neural network method is proposed based on our previous work for microcalcification detection [12], Kalman Filtering technique realized by the PI's group [12] will be used as a powerful tool for training a NN required for large number of input nodes and complex structures. The NN will have two stages to include input of implicit and explicit features at each stage, using previous experience in feed-forward NN's and backpropagation training as in [12].

Key Research Accomplishments

(1) Well done the whole system design and optimization.
(2) Well done the enhancement module including multiresolution microcalcification cluster enhancement.
(3) Well done the grouping criteria design for identification of microcalcification clusters.
(4) Well done the adaptive method design for MCCs segmentation module.
(5) Well done the feature extraction and analysis module including implicit feature and explicit features for digital mammograms.
(6) Well done the correlation analysis for inter-projection features.
(7) Well done the classification module design for classification of MCCs versus normal cases of mammograms.

Reportable Outcomes

---Manuscripts, abstracts, presentations;

1. Wei Qian, Dansheng Song, Xuejun Sun, "Multistage statistical order with neural network for false positive reduction in full field digit mammography" on Nonlinear Signal and Image Processing June 3-6, 2001 Baltimore, USA

2. Wei Qian, Xuejun Sun, Dansheng Song, Robert A. Clark, "Digital mammography: Wavelet Transform and Kalman Filtering Neural Network in Mass Segmentation and Detection" Accepted by Academic Radiology, 2001

3. Wei Qian, Xuejun Sun, Dansheng Song, Robert A. Clark, "A Novel Hybrid Filter Architecture for Image Enhancement and Detection in Digital Mammography", Submitted to Computerized Medical Imaging and Graphics, 2001

4. L. Zhang, W. Qian, R.Sankar, D. Song, R.Clark, 'A New False Positive Reduction Method for MCCs Detection in Digital Mammography', International conference on acoustics speech, and signal processing May 7-11,2001 Salt Lake city, Utah

5. Dansheng Song, Wei Qian, Xuejun Sun, and Robert A Clark, "Neural Network for False Positive Reduction in Full Field Digital Mammography with Microcalcification Shape preservation," SPIE Multispectral Image Processing and Pattern Recognition, 22-24 Oct. 2001 Wuhan, China

------ Degree obtained that are supported by this award ;

Lin Zhang, got Master degree in March of 2001, He is currently working in CISCO Inc. in California.

Jie Lin, Working on Master degree, Will be finished in July of 2002.

------Funding applied for based on the work supported by this award;

Proposal Submitted to Agency: NIH, R01 on 02/01/21
A Telemammography Network for Underserved Area

Proposal Submitted to Agency: U.S. Army Medical Research and Materiel Command DOD 2001 Breast Cancer Research Program

1. Title: Telemedicine and Telemammography Using a Satellite Network for Remote Areas Including Oversea U.S. Military Bases

2. Title: Full Optimization of CAD System for Clinical Application

3. Title: A New CAD Scheme for the Detection of Tiny Mass Using Ipsilateral Multi-View Mammograms

Conclusion

In the second year of the project, we successfully completed the design and optimization of our MCCs detection system which includes the following five-step paradigm: (1) breast area segmentation and artifact elimination, (2) MCC structure and normal tissue enhancement, (3) suspicious MCC area segmentation or localization, (4) feature extraction and analysis of suspicious areas, and (5) suspicious area classification as normal or abnormal. The full evaluation and further optimization is planned for the coming budget year.

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[1] Wei Qian, Dansheng Song, Xuejun Sun, "Multistage statistical order with neural network for false positive reduction in full field digit mammography" on Nonlinear Signal and Image Processing June 3-6, 2001 Baltimore, USA

[2] Wei Qian, Xuejun Sun, Dansheng Song, Robert A. Clark, "Digital mammography: Wavelet Transform and Kalman Filtering Neural Network in Mass Segmentation and Detection" Accepted by Academic Radiology, 2001

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Appendices

Key Research Accomplishments

(1) Well done the whole system design and optimization.
(2) Well done the enhancement module including multiresolution microcalcification cluster enhancement.
(3) Well done the grouping criteria design for identification of microcalcification clusters.
(4) Well done the adaptive method design for MCCs segmentation module.
(5) Well done the feature extraction and analysis module including implicit feature and explicit features for digital mammograms.
(6) Well done the correlation analysis for inter-projection features.
(7) Well done the classification module design for classification of MCCs versus normal cases of mammograms.

Reportable Outcomes

---Manuscripts, abstracts, presentations;

1. Wei Qian, Dansheng Song, Xuejun Sun, "Multistage statistical order with neural network for false positive reduction in full field digit mammography" on Nonlinear Signal and Image Processing June 3-6, 2001 Baltimore, USA

2. Wei Qian, Xuejun Sun, Dansheng Song, Robert A. Clark, "Digital mammography: Wavelet Transform and Kalman Filtering Neural Network in Mass Segmentation and Detection" Accepted by Academic Radiology, 2001

3. Wei Qian, Xuejun Sun, Dansheng Song, Robert A. Clark, "A Novel Hybrid Filter Architecture for Image Enhancement and Detection in Digital Mammography", Submitted to Computerized Medical Imaging and Graphics, 2001

4. L. Zhang, W. Qian, R.Sankar, D. Song, R.Clark, 'A New False Positive Reduction Method for MCCs Detection in Digital Mammography', International conference on acoustics speech, and signal processing May 7-11,2001 Salt Lake city, Utah

5. Dansheng Song, Wei Qian, Xuejun Sun, and Robert A Clark, "Neural Network for False Positive Reduction in Full Field Digital Mammography with Microcalcification Shape preservation," SPIE Multispectral Image Processing and Pattern Recognition, 22-24 Oct. 2001 Wuhan, China

------ Degree obtained that are supported by this award ;

Lin Zhang, got Master degree in March of 2001, He is currently working in CISCO Inc. in California.

Jie Lin, Working on Master degree, Will be finished in July of 2002.

------**Funding applied for based on the work supported by this award;**

Proposal Submitted to Agency: NIH, R01 on 02/01/21
A Telemammography Network for Underserved Area

Proposal Submitted to Agency: U.S. Army Medical Research and Materiel Command DOD 2001 Breast Cancer Research Program

1. Title: Telemedicine and Telemammography Using a Satellite Network for Remote Areas Including Oversea U.S. Military Bases

2. Title: Full Optimization of CAD System for Clinical Application

3. Title: A New CAD Scheme for the Detection of Tiny Mass Using Ipsilateral Multi-View Mammograms

Academic
RADIOLOGY

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June 18, 2001

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RE: Manuscript # 01-046

Dear Dr. Qian:

Thank you for submitting your revised manuscript, "Digital Mammography: Wavelet Transform and Kalman Filtering Neural Network in Mass Segmentation and Detection," to *Academic Radiology*. We are pleased to accept it for publication .

We anticipate that it will be published in 11/1/2001, though changes may occur which could alter this schedule. Your manuscript will be forwarded to the RSNA offices for copy editing and further processing. You will then receive "author queries" to review a few weeks later.

Although your manuscript has been accepted for publication, we are required to have on file a signed Publication Agreement for each submission. Please read and sign the enclosed form and return it to the editorial office at your earliest convenience.

Further correspondence may be made to the address above, or via electronic mail to us at academic-radiology@oasis.rad.upenn.edu. Please refer to manuscript number 01-046 when making inquiries.

Sincerely,

Stanley Baum, M.D.